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## Featured Article

# Tolerability of ORM-12741 and effects on episodic memory in patients with Alzheimer's disease

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**Abstract**

**Introduction:** ORM-12741 is a novel selective antagonist of alpha-2C adrenoceptors. This trial evaluated the safety and efficacy of ORM-12741 in patients with Alzheimer's disease (AD).

**Methods:** A randomized, double-blind, placebo-controlled, exploratory phase 2a trial was conducted in 100 subjects with AD and neuropsychiatric symptoms. Participants were randomized to receive one of two flexible doses of ORM-12741 (30–60 mg or 100–200 mg) or placebo b.i.d. for 12 weeks in addition to standard therapy with cholinesterase inhibitors. Efficacy was assessed primarily with the Cognitive Drug Research (CDR) computerized assessment system and secondarily with the Neuropsychiatric Inventory (NPI).

**Results:** A statistically significant treatment effect was seen in one of the four primary CDR system end points, Quality of Episodic Memory ( $P = .030$ ; not adjusted for multiple comparisons), favoring ORM-12741 over placebo. NPI caregiver distress scores also favored ORM-12741 ( $P = .034$ ). ORM-12741 was well tolerated.

**Discussion:** This is the first clinical trial providing evidence on an acceptable safety profile for ORM-12741 in patients with AD and neuropsychiatric symptoms. In addition, the trial provided hints of potential therapeutic benefit, primarily on episodic memory, in this patient population.

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**Keywords:**

Alzheimer's disease; Cognition; Memory; Alpha-2C adrenoceptor antagonist; ORM-12741; Randomized trials; Behavioral and psychological symptoms of dementia; Neuropsychiatric symptoms

**1. Introduction**

Alzheimer's disease (AD) is the most common cause of dementia and a major cause of morbidity and mortality. Current approved drug treatments for AD include cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the N-methyl-D-aspartate receptor antagonist memantine. The effects of these medications are symptomatic and efficacy is considered to be modest [1]. Many patients have neuropsychiatric symptoms (NPSs) in the course of their cognitive decline, and there are no approved treatments that can be recommended for long-term use for these important comorbid conditions. There is an urgent need

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for better treatment alternatives targeting cognitive impairment as well as NPS in patients with AD [1–3].

According to a recent analysis of the AD drug development pipeline, there were 24 compounds in phase 3 and 45 compounds in phase 2 clinical trials [4]. Most of the molecules that are being developed for AD are aiming for disease modification. However, as it is unlikely that any of the compounds now in clinical development will be able to totally prevent the development of dementia in all patients, symptomatic therapies will still be needed for a long time.

Alpha-2 adrenoceptors (ARs) are distributed throughout the central nervous system and peripheral tissues and mediate many physiological and pharmacological actions of endogenous catecholamines. Alpha-2 ARs consist of three distinct subtypes, alpha-2A, alpha-2B, and alpha-2C, each encoded by its own gene. Current knowledge suggests that the majority of classical alpha-2 adrenergic agonist actions (such as sedation, analgesia, and bradycardia) are mediated by the alpha-2A AR, whereas the other subtypes act as “fine-tuners” of related functions and may sometimes mediate opposite functional effects [5]. The highest densities of alpha-2C ARs are found in the ventral and dorsal striatum and in the hippocampus. Alpha-2C ARs may play an important role in the modulation of dopamine and serotonin neurotransmission in the brain [6]. These effects seem to be especially prominent under stressful conditions [6]. At the behavioral level, alpha-2C ARs modulate the performance of experimental animals in tests predicting antidepressant and antipsychotic efficacy as well as learning and memory functions [6]. Consistent with this, specific and subtype-selective alpha-2C AR antagonists have shown positive effects in various nonclinical models predicting efficacy on cognition as well as symptoms of schizophrenia and depression [7,8].

ORM-12741 is a potent, specific, and subtype-selective alpha-2C AR antagonist that was well tolerated in phase I studies (Orion Pharma, unpublished results; for study design information, see NCT00693316, NCT00792493, NCT00817544, NCT00818740, NCT00831077, NCT01068028). Its pharmacokinetic properties make ORM-12741 suitable for oral use, and the compound has demonstrated concentration-dependent alpha-2C AR occupancy in vivo in the human brain (Lovro et al., unpublished results; see NCT00829907), as investigated with positron emission tomography (PET) imaging [9–11].

The primary objectives of this study were to evaluate the safety and tolerability of ORM-12741 and the efficacy of ORM-12741 on cognitive performance in patients with AD receiving standard cholinesterase inhibitor therapy. The secondary objectives of the study were to evaluate the efficacy of ORM-12741 on NPS.

## 2. Methods

### 2.1. Participants

Male and female subjects aged 55–90 years with a diagnosis of probable AD according to National Institute of Neurological

and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [12] and Dementia of the Alzheimer's Type according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text Revision (DSM-IV-TR) [13] criteria were recruited. All study subjects were required to have a history of progressive cognitive deterioration, brain imaging consistent with AD, a Mini-Mental State Examination (MMSE) score of 12–21, a 10-item Neuropsychiatric Inventory (NPI) [14] total score  $\geq 15$  and stable usage of cholinesterase inhibitors at standard doses for at least 2 months. Use of memantine and/or serotonin reuptake inhibitors was also allowed, if on stable doses. All study subjects were required to have a committed caregiver who was able and willing to assist them with medications and provide study subject information.

Key exclusion criteria were any type of dementia other than AD, modified Hachinski ischemia score of  $>4$ , a history or evidence of any other significant disease that could impair cognition, and residence in a skilled nursing facility. Subjects who were not able to complete the CDR system tests ([www.bracketglobal.com](http://www.bracketglobal.com)) after a training session were excluded. Subjects who had used antipsychotics or anticholinergics within the previous 2 months were also excluded.

### 2.2. Study design

This double-blind, placebo-controlled, parallel-group exploratory clinical phase 2a trial was conducted between April 2011 and September 2012 at 18 clinical sites in Finland, Poland, Romania, and Spain.

Study participants were equally randomized into three parallel groups to receive one of two flexible dose levels of ORM-12741 (30–60 mg or 100–200 mg) or placebo orally twice a day for 12 weeks in addition to their stable cholinesterase inhibitor therapy (donepezil, rivastigmine, or galantamine) through a central interactive Web-response system according to a computer-generated, randomized allocation schedule. Randomization was stratified according to the MMSE score (12–16 vs. 17–21). The low-dose group received 30 mg for the first week and 60 mg in subsequent weeks; the high-dose group received 100 mg for the first week and 200 mg in subsequent weeks. The investigators were permitted to reduce the dose to the starting dose if the higher dose was poorly tolerated. Blinding was accomplished with the use of placebo capsules that were identical in appearance to the ORM-12741 capsules. Dose increases and reductions were similarly performed in the placebo group.

### 2.3. Outcomes

#### 2.3.1. Efficacy

The nine core tests of the CDR system for patients with dementia were used to assess efficacy [15]. These tests comprised simple reaction time, choice reaction time, digit vigilance, numeric and spatial working memory, immediate and delayed

word recall, and word and picture recognition. The four prespecified primary efficacy outcomes for cognitive performance were changes from baseline to week 12 in the CDR System standard composite domain factor scores [16]: Quality of Episodic Memory, Quality of Working Memory, Power of Attention and Speed of Memory Retrieval, as also used previously in many dementia trials [17–19]. Furthermore, a prespecified composite score for Continuity of Attention was calculated and additionally, a Quality of Memory composite score, combining the accuracy scores from all working and episodic memory tasks, was calculated after unblinding the treatment assignment to further characterize the effects of ORM-12741 [16]. After two training sessions at the screening visit, each subject completed the CDR system tasks at baseline and at the weeks 1, 2, 4, 8, and 12 visits about 1 hour after the morning dose, near the anticipated maximum plasma concentration of ORM-12741.

Secondary efficacy for NPS was assessed by the NPI rating scale [14], including the 10-item NPI total score and NPI caregiver distress score. The NPI was assessed at screening, at baseline and at weeks 4 and 12.

Other exploratory efficacy outcome measures were the Controlled Oral Word Association Test (COWAT) [20], Category Fluency Test (CFT) [21], Cornell Scale for Depression in Dementia (CSDD) [22], Clinical Global Impression of Change (CGI-C) [23], and self-rated Cognitive Failures Questionnaire (CFQ) [24].

### 2.3.2. Pharmacokinetics

Pharmacokinetic blood samples were collected at baseline and before the morning dose of study medication at weeks 1, 2, 4, 8, and 12. Plasma concentrations of ORM-12741 and cholinesterase inhibitors were determined using validated methods based on liquid chromatography–tandem mass spectrometry.

### 2.3.3. Safety

Safety was assessed at each visit by adverse events, blood pressure, heart rate, 12-lead ECG, and laboratory tests. Blood pressure and heart rate were recorded in supine position before and 1 and 2 hours after the morning dose, followed by orthostatic test measurements after 3 minutes of standing. Physical examinations were performed during screening, at baseline and at weeks 4 and 12.

### 2.4. Statistical analysis

The sample size for this exploratory phase 2a trial was based on practical consideration, and no formal power calculations were performed. The primary efficacy assessment was performed on the modified intention-to-treat population, defined as subjects who received at least one dose of study medication and had completed baseline assessments and at least one post-baseline CDR system test session.

All statistical tests were two sided with a 0.05 level of significance. No adjustments were made for multiple comparisons. A mixed-effects model for repeated measurements with 95% confidence intervals (CIs) was used to compare changes in the continuous primary and secondary outcomes. The models included treatment, time point and treatment by time point interaction as fixed effects, study site as a random effect, and baseline value of the outcome variable in question as a covariate. Least squares means (LS means) and standard error (SE) of means were calculated for effects of treatment and treatment by time point interaction. In addition, effect sizes were calculated using Cohen's *d* method [25]. The residual error term was used, and the square root of this was used as the denominator, and the differences in LS means between placebo and active conditions were used as the numerator. The categorical outcome measure, CGI-C, was compared with the generalized linear model and 95% CIs. One-way analysis of variance, the  $\chi^2$  test and Fisher exact test were

Table 1  
Baseline characteristics of the study participants

Baseline characteristic	Placebo ( <i>N</i> = 34)	ORM-12741, 30–60 mg ( <i>N</i> = 33)	ORM-12741, 100–200 mg ( <i>N</i> = 33)	Total ( <i>N</i> = 100)
Sex, <i>n</i> (%)				
Female	17 (50.0)	19 (57.6)	23 (69.7)	59 (59.0)
Male	17 (50.0)	14 (42.4)	10 (30.3)	41 (41.0)
Age, years	72.3 (8.5)	71.8 (8.2)	71.8 (6.8)	72.0 (7.8)
MMSE score	18.1 (2.7)	18.6 (2.4)	19.0 (2.5)	18.5 (2.6)
NPI total score	22.7 (11.7)	21.2 (7.7)	19.0 (7.6)	21.0 (9.3)
NPI caregiver distress score	10.4 (6.8)	10.6 (5.4)	9.8 (4.3)	10.2 (5.6)
Age at diagnosis of AD, years	71.2 (8.3)	70.6 (7.8)	70.5 (6.8)	70.8 (7.6)
Duration of AD, years	1.6 (1.4)	1.7 (1.6)	1.9 (1.4)	1.7 (1.5)
Use of cholinesterase inhibitors and memantine, <i>n</i> (%)				
Donepezil	23 (67.6)	20 (60.6)	22 (66.7)	65 (65.0)
Galantamine	2 (5.9)	2 (6.1)	1 (3.0)	5 (5.0)
Rivastigmine	9 (26.5)	11 (33.3)	10 (30.3)	30 (30.0)
Memantine	5 (14.7)	3 (9.1)	3 (9.1)	11 (11.0)
Duration of cholinesterase inhibitor and memantine therapies, years				
Cholinesterase inhibitors	1.5 (1.4)	1.6 (1.5)	1.6 (1.4)	1.6 (1.5)
Memantine	1.3 (0.7)	1.6 (0.8)	0.9 (0.6)	1.3 (0.7)

Abbreviations: AD, Alzheimer disease; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; SD, standard deviation.

NOTE. Values are mean (SD) unless otherwise stated. None of the comparisons between the treatment groups was statistically significant.

used to evaluate possible differences between the treatment groups in the subjects' baseline characteristics (Table 1).

### 2.5. Protocol approvals, consents, and registrations

Permission to conduct the study was received from each national regulatory agency before commencement. The study protocol and amendments were approved by an ethics committee at each clinical site. Written informed consent was obtained from all study subjects and their caregivers. This study was conducted in compliance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice Guidelines and is registered on [Clinicaltrials.gov](https://clinicaltrials.gov) (NCT01324518).

## 3. Results

### 3.1. Participants

Of the 132 subjects screened for the study, 100 subjects were randomized and 91 subjects completed the study. All randomized subjects were included in the efficacy and safety analyses. Fig. 1 summarizes subject enrollment and participation.

Baseline characteristics were similar in the three treatment groups (Table 1). The mean subject age was 72 years (range 55–90); 59% were female. Ninety-nine subjects (99%) were Caucasian and one subject was Hispanic. All subjects used cholinesterase inhibitors and 11 subjects (11%) used memantine for the treatment of AD. Antidepressants were used by 12 (36%), 10 (30%), and 10 (29%) subjects in the low-dose, high-dose, and placebo groups, respectively.

Dose adjustments were allowed for tolerability. Study treatment dosage was reduced for 8 subjects (8%): for two subjects from ORM-12741 60–30 mg, for three subjects from ORM-12741 200–100 mg, and for three subjects the placebo dose was reduced to half.

### 3.2. Cognitive performance

Compared to placebo, statistically significant treatment effects favoring active treatment were observed on Quality of Episodic Memory composite scores over 12 weeks of treatment, with no clear differences between the two dose levels of ORM-12741 (Fig. 2). The Quality of Episodic Memory composite scores decreased from baseline to week 12 by a mean (SD) of  $-32.4$  (50.6) points in the placebo group, increased by  $4.6$  (51.5) points in the low-dose

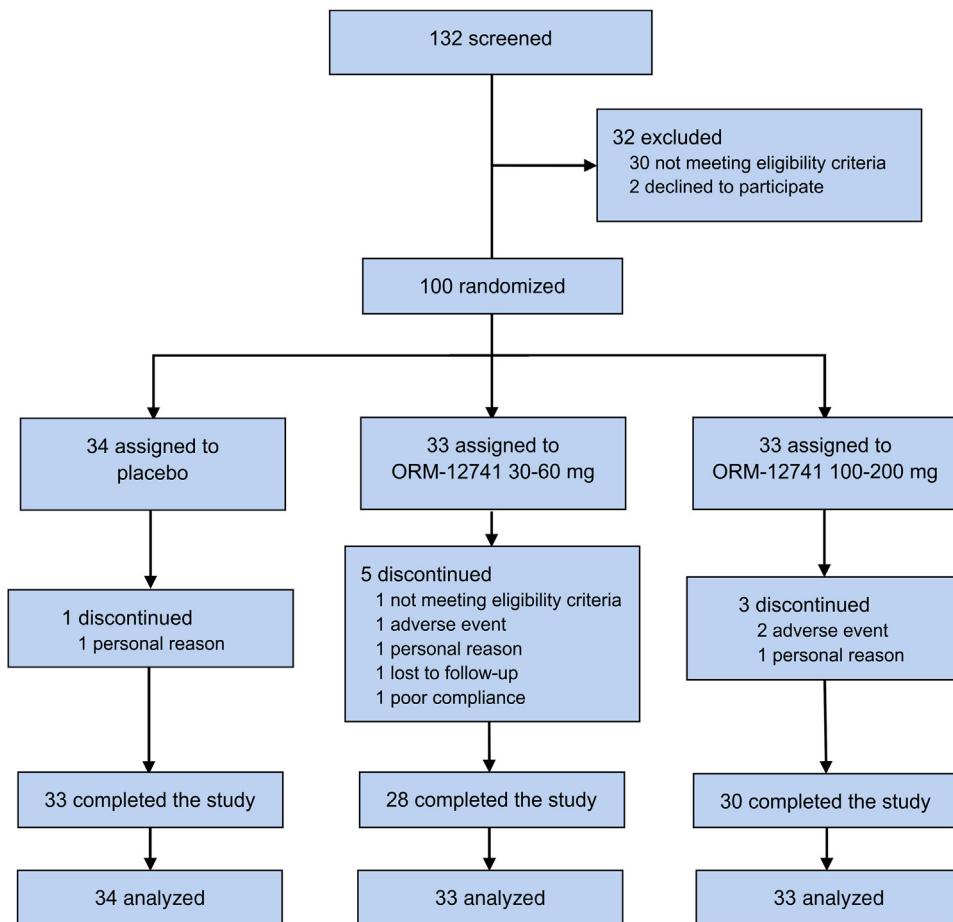


Fig. 1. Disposition of subjects.



group and increased by 5.2 (42.5) points in the high-dose group. The overall treatment effect for the Quality of Episodic Memory composite score was statistically significant ( $P = .030$ ). In pairwise comparisons, both dose levels of ORM-12741 showed statistically significant efficacy over placebo. The estimated treatment difference was 16.5 points (95% CI 0.28 to 32.63,  $P = .046$ ) for the low dose versus placebo and 20.6 points (95% CI 4.57 to 36.7,  $P = .012$ ) for the high dose versus placebo (Table 2). The Cohen's  $d$  effect size was 1.09 for the low dose versus placebo and 1.02 for the high dose versus placebo at 12 weeks.

The overall treatment effect was not statistically significant ( $P = .193$ ) for the Quality of Working Memory composite score. The low dose showed an overall trend for improving Working Memory over the 12 weeks of treatment (Fig. 2). The estimated treatment difference was 0.16 points (95% CI  $-0.02$  to  $0.33$ ,  $P = .079$ ) for the low dose versus placebo and 0.11 points (95% CI  $-0.06$  to  $0.28$ ,  $P = .219$ ) for the high dose versus placebo (Table 2). The effect size was 0.88 for the low dose versus placebo and 0.55 for the high dose versus placebo at 12 weeks.

The most marked difference between ORM-12741 and placebo was seen in the post hoc-calculated Quality of Memory composite score that combines all of the accuracy measures from the six tests included in the Quality of Episodic and Working Memory composite scores. The overall treatment effect was statistically significant ( $P = .034$ ) over the 12 weeks of treatment, with subjects in both ORM-12741 dose groups improving on Quality of Memory and subjects on placebo showing a steady decline. The estimated treatment difference was 37.4 points (95% CI 10.9–63.9,  $P = .006$ ) for the low dose versus placebo and 31.1 points (95% CI 5.19 to 57.1,  $P = .019$ ) for the high dose versus placebo (Table 2). The effect size was 1.54 for the low dose versus placebo and 1.12 for the high dose versus placebo at 12 weeks.

No statistically significant treatment effect was detected in the other composite cognitive domain scores of Speed of Memory, Power of Attention, or Continuity of Attention (Table 2).

### 3.3. Neuropsychiatric symptoms

A statistically significant ( $P = .034$ ) treatment effect in favor of ORM-12741 was observed for the NPI caregiver distress score. The NPI caregiver distress score decreased by a mean (SD) of  $-2.4$  (4.8) points in the low-dose group and by  $-2.1$  (3.4) points in the high-dose group. No change was observed (mean 0.4, SD 4.9) in the placebo group (Fig. 3). The estimated treatment difference was  $-2.13$  points (95% CI  $-3.92$  to  $-0.35$ ,  $P = .020$ ) for the low dose versus placebo and  $-1.94$  points (95% CI  $-3.7$  to  $-0.18$ ,  $P = .031$ ) for the high dose versus placebo. The effect size was  $-1.22$  for the low dose versus placebo and  $-0.96$  for the high dose versus placebo at 12 weeks.

No statistically significant treatment effects were seen in the NPI total score (Fig. 3). However, a numerical trend for

improvement was seen in the low-dose group compared to placebo.

### 3.4. Additional efficacy end points

No statistically significant treatment effects were detected between active treatment and placebo for COWAT, CFT, CSDD, CFQ (Supplementary Table 1), or the CGI-C (Supplementary Table 2).

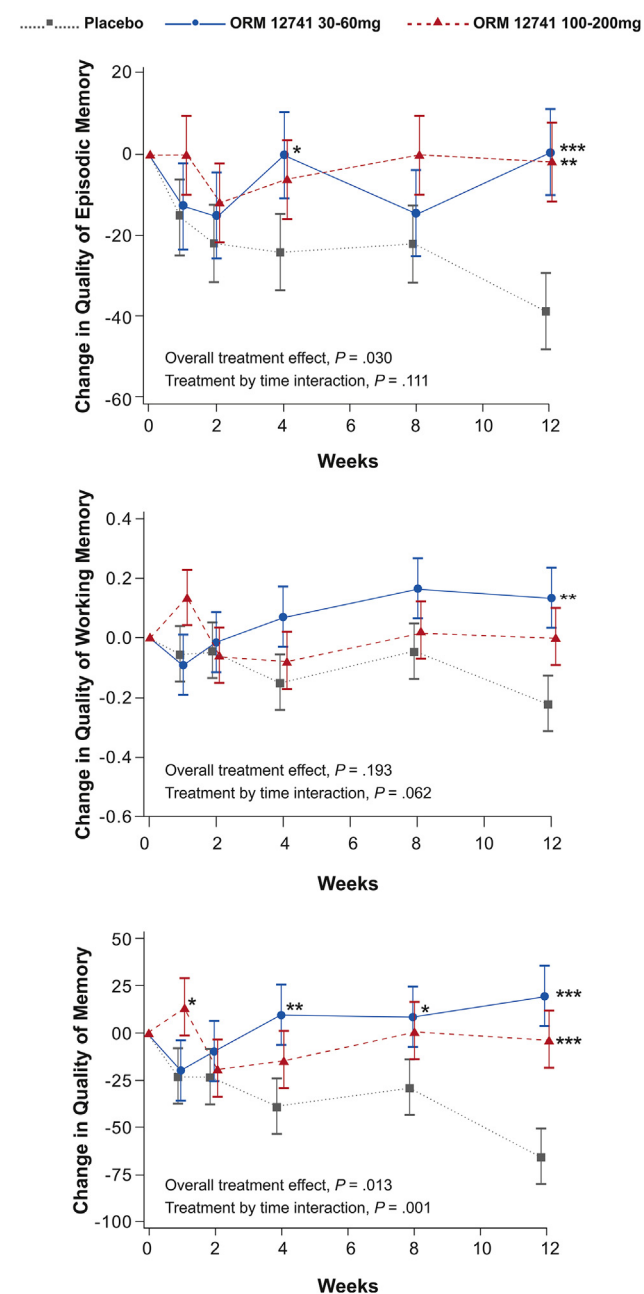


Fig. 2. Quality of Episodic Memory, Quality of Working Memory, and Quality of Memory CDR composite scores. Data are presented as LS means (SE) for changes from baseline. A positive change from baseline indicates improvement. \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$  for difference versus placebo at time point. Abbreviations: CDR, Cognitive Drug Research; LS means, least squares means; SE, standard error.

Table 2  
Estimated treatment differences of ORM-12741 versus placebo over 12 weeks of treatment

Estimated treatment differences of SRM 127-11 versus placebo over 12 weeks of treatment			
Variable	Baseline mean (SD)	Overall treatment effect	Estimated treatment difference versus placebo (95% CI)
Quality of Episodic Memory			
Placebo	82.7 (54.8)	$P = .030$	
Low dose	93.2 (67.0)		16.5 (0.28 to 32.63), $P = .046$
High dose	77.8 (59.0)		20.6 (4.57 to 36.7), $P = .012$
Quality of Working Memory			
Placebo	1.07 (0.59)	$P = .193$	
Low dose	1.01 (0.68)		0.16 (−0.02 to 0.33), $P = .079$
High dose	1.16 (0.48)		0.11 (−0.06 to 0.28), $P = .219$
Quality of Memory			
Placebo	185 (100)	$P = .013$	
Low dose	188 (111)		37.4 (10.9 to 63.9), $P = .006$
High dose	190 (88.3)		31.1 (5.19 to 57.1), $P = .019$
Speed of Memory			
Placebo	9801 (7563)	$P = .654$	
Low dose	9928 (5595)		−147 (−1267 to 973), $P = .795$
High dose	9940 (7170)		359 (−740 to 1457), $P = .518$
Power of Attention			
Placebo	2199 (1049)	$P = .708$	
Low dose	2061 (736)		58.7 (−195 to 312), $P = .646$
High dose	2085 (1092)		−48.7 (−303 to 205), $P = .704$
Continuity of Attention			
Placebo	80.4 (18.4)	$P = .957$	
Low dose	82.4 (14.7)		−0.38 (−3.97 to 3.20), $P = .833$
High dose	84.7 (14.8)		−0.52 (−4.09 to 3.06), $P = .775$

Abbreviations: CI, confidence interval; SD, standard deviation.

### 3.5. Pharmacokinetics

ORM-12741 did not accumulate during the 12 weeks of treatment. Steady-state concentrations were reached after 2 weeks of treatment. The mean (SD) plasma trough concentration was 18.4 (13.9) ng/mL for the low dose and 61.0 (45.9) ng/mL for the high dose at week 12. ORM-12741 did not have significant effects on the concentrations of cholinesterase inhibitors (data not shown).

### 3.6. Safety

There were no notable differences in the frequency of adverse events among the three groups (Table 3). One subject experienced cholestasis with asymptomatic high liver enzyme values after 4 weeks of high-dose treatment. This was reported as a serious adverse event and the subject discontinued the trial. All adverse events are presented by system organ class and preferred term in Supplementary Table 3.

There were no clinically meaningful changes from baseline in the mean safety laboratory values. Standing heart rate values in the high-dose group were slightly above than those in the placebo group. However, no statistically significant treatment effect was observed (the estimated LS mean for difference was at most +4.3 bpm in the high-dose group compared to the placebo group 1 hour after dosing at week 1). No clinically meaningful changes were seen in blood pressure and 12-lead ECG variables, including the QTc interval.

## 4. Discussion

This phase 2a proof-of-concept clinical trial was conducted to evaluate the safety and efficacy of two dose levels of ORM-12741 (30–60 mg and 100–200 mg) compared to placebo for 12 weeks in patients with AD and NPS, all receiving standard cholinesterase inhibitor therapy. Statistically significant positive treatment effects were noted for both ORM-12741 dose levels compared to placebo on the prespecified efficacy analyses for the Quality of Episodic Memory composite score of the CDR cognitive battery. This was supported by a consistently positive trend for the Quality of Working Memory composite score, which consist of subscores assessed independently from the Quality of Episodic Memory composite score. Positive treatment effects were noted also for the post hoc-calculated Quality of Memory composite score that combines subscores relating to both episodic and working memory. No clear differences in efficacy between the two active dose groups were seen. Performance in the other cognitive tests did not differ significantly between ORM-12741 and placebo.

The placebo group showed gradually increasing impairment over the 12-week trial duration on memory composite scores. This was not observed in the active-treated subjects, whose performance was maintained at baseline levels. No earlier published data are available on the progression of AD as measured by CDR system composite scores in a patient population with moderate AD and NPS, such as that used in the present trial. However, the Quality of Episodic Memory composite score has previously been shown to decline significantly

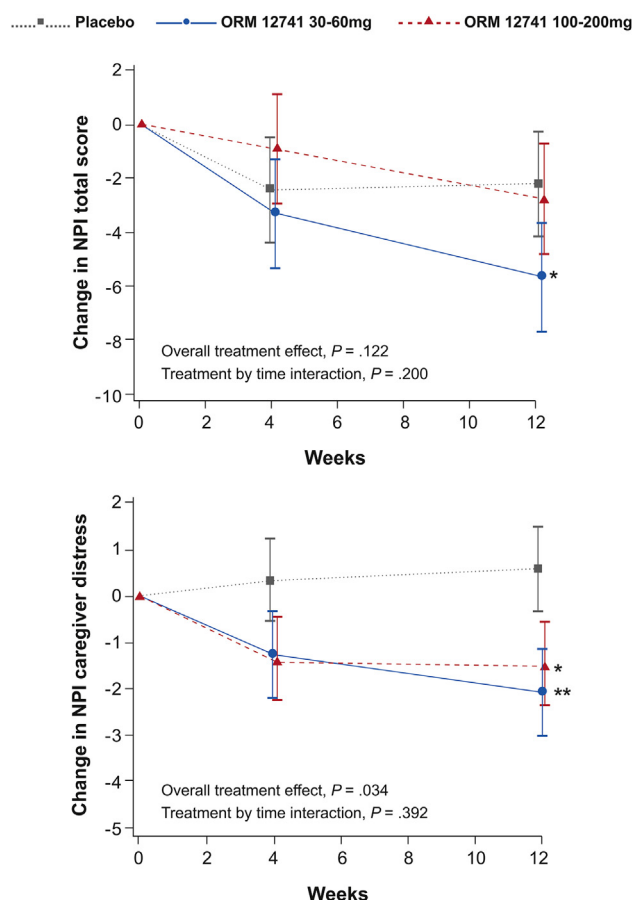


Fig. 3. NPI total and NPI caregiver distress scores. Data are presented as LS means (SE) for changes from baseline. A negative change from baseline indicates improvement. \* $P < .05$ , \*\* $P < .01$  for difference versus placebo at time point. Abbreviations: LS means, least squares means; NPI, Neuropsychiatric Inventory; SE, standard error.

over 3 months in a placebo-treated population in a large therapeutic AD trial [26], AD patients with NPS have been shown to progress faster than patients without NPS [27], and moderately impaired AD patients decline more quickly than do mildly impaired ones [28], consistent with the significant decline in

memory measures of the placebo-treated patients seen in the present trial. The pattern of response in the active treatment groups and the rate of decline in the placebo group closely resemble those seen in some cholinesterase inhibitor registration trials [29] but differs from certain other trials where clear initial improvement in cognitive performance have been seen with symptomatic treatments [30,31]. This may be speculated to be due to differences in study populations, background treatments (particularly cholinesterase inhibitors), and used efficacy measures.

Quality of Episodic Memory has been shown to be in good agreement with the Alzheimer's Disease Assessment Scale–cognitive score (ADAS-Cog;  $r = 0.7$ ) [32]. The effect sizes of ADAS-Cog improvements with the three currently approved cholinesterase inhibitors in their registration trials have a median value of 0.28 at the higher used dose levels [28], which is considerably smaller than the estimated effect size for improvement seen in the present trial. This suggests that the benefits seen with ORM-12741 in the present trial are clinically meaningful.

Both ORM-12741 dose levels were clearly and statistically significantly superior to placebo in reducing NPI caregiver distress scores during the 12-week treatment period. However, no significant effect was seen in the NPI total score, although numerically, NPI total scores also favored the ORM-12741 low-dose group versus placebo.

The observed effects are consistent with predictions from animal efficacy models where alpha-2C AR antagonists have shown beneficial effects on learning and memory functions, as well as antidepressant and antipsychotic properties [7,8]. However, the present trial involved only a small number of participants, and the duration of the study was short. Due to the exploratory nature of this phase 2a trial, the reported  $P$ -values were not corrected for multiple comparisons. In addition, the decrease that was seen in the memory measures was relatively large in the placebo group, and no earlier results have been published using the same outcome variables in a similar patient population. Therefore, the efficacy results should be regarded as tentative, and

Table 3  
Subjects experiencing adverse events

Adverse events	Placebo ( $N = 34$ )	ORM-12741, 30–60 mg ( $N = 33$ )	ORM-12741, 100–200 mg ( $N = 33$ )
Any AE	21 (61.8)	18 (54.5)	21 (63.3)
Any related AE	6 (17.6)	8 (24.2)	10 (30.3)
Any serious AE	0	0	1 (3.0)
Discontinuation due to an AE	0	1 (3.0)	2 (6.1)
Dose reduction due to an AE	3 (8.8)	2 (6.1)	3 (9.1)
AEs in $\geq 5$ subjects overall			
Headache	4 (11.8)	2 (6.1)	1 (3.0)
Urinary tract infection	3 (8.8)	1 (3.0)	5 (15.2)
Nausea	3 (8.8)	2 (6.1)	1 (3.0)
Vomiting	1 (2.9)	1 (3.0)	4 (12.1)
Diarrhea	2 (5.9)	2 (6.1)	1 (3.0)
Irritability	3 (8.8)	0	2 (6.1)

Abbreviation: AE, adverse event.

NOTE. Values are  $n$  (%).



replication of the findings in larger populations will be necessary for definitive conclusions on safety and efficacy.

ORM-12741 did not accumulate during the 12-week treatment period. The measured trough concentrations of ORM-12741 in the plasma of elderly subjects with AD were of similar magnitude as previously observed at steady state after similar dose levels in healthy volunteer subjects (Orion Pharma, unpublished data). Based on this and the results of the receptor occupancy study (Lovro et al., unpublished data), it can be assumed that maximal alpha-2C AR occupancy in the brain was reached by both dose levels after dosing. Overall, there was no clear separation between the two dose levels of ORM-12741 regarding memory benefits or NPI scores, although the low-dose group performed numerically slightly better on some of the measures. When the alpha-2C AR PET occupancy data are taken into account, it seems likely that maximal effects were reached with both dose levels.

The safety profile in each treatment arm was considered acceptable and no significant safety concerns were revealed. The subjects in the high-dose group reported more treatment-related AEs than the subjects in the low-dose and placebo groups. However, the number of subjects with each specific AEs was small, and no clear differences in the AE profiles were seen between the treatments. One case of cholestasis was reported as a serious adverse event in the high-dose group.

In conclusion, both investigated ORM-12741 doses showed hints of superior efficacy compared to placebo in a validated measure of episodic memory in subjects with AD receiving standard cholinesterase inhibitor therapy in this 12-week proof-of-concept trial. No differences in efficacy were observed between the two investigated dose levels of ORM-12741. This is the first clinical trial providing favorable safety data and hints of potential therapeutic benefit for this novel mechanism of action in AD patients.

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## Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.trci.2016.11.004>.

## RESEARCH IN CONTEXT

1. Systematic review: The authors searched PubMed for the distribution and role of alpha-2C adrenoceptors in the brain and the effects of selective alpha-2C adrenoceptor antagonists in experimental animals. Relevant research is cited. The literature suggests that alpha-2C adrenoceptor antagonists improve cognition and have antipsychotic and antidepressant properties. However, no previous clinical trials with alpha-2C adrenoceptor antagonists have been reported in patients with Alzheimer disease (AD).
2. Interpretation: This is the first clinical trial providing evidence on an acceptable safety profile and hints of potential therapeutic effects of an alpha-2C adrenoceptor antagonist in patients with AD.
3. Future directions: Replication of the findings in a larger study population will be important. Efficacy on both cognition and neuropsychiatric symptoms should be further investigated.

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